REMARKS

Claims 1-9, 11-17 and 59-70 presently appear in this case. No claims have been allowed. The official action of April 11, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method of altering gene expression in a population of human embryonic stem cells by introducing into the population of human embryonic stem cells a polynucleotide that contains a gene expression altering sequence. It is possible to obtain a transfection efficiency greater than that obtainable by means of electroporation by use of an appropriate transfection reagent.

Claims 1-9, 22-17 and 59-61 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that this is a new matter rejection. The examiner considers that the amendment to the claims reciting that the method of altering gene expression requires a transfection efficiency greater than that obtainable by means of electroporation introduces new matter into the disclosure. The examiner states that the citations to the specification that applicants point to fail to describe the as amended claims, such that one of skill in the art would recognize that applicants had

possession of the claimed invention. While the examiner recognizes that paragraph 43 of the specification recites that utilizing cationic polymers produced improved results of transfection over electroporation, the only example that shows this is ExGen500. The examiner states that to the extent that the claims encompass other transfection reagents, this constitutes new matter. This rejection is respectfully traversed.

As explained in detail in applicant's amendment of December 27, 2006, the present specification as filed clearly indicated that, in its broadest aspect, the present invention included transfecting the cells in any manner, such as by means of a cationic polymer transfection reagent or by electroporation. However, in paragraph [0043], the present specification clearly states that, while electroporation was found to be the method of choice for introducing foreign DNA into murine ES-cells, the present inventors had found that, although human ES-cells can be transfected by electroporation, improved results were obtained by transfection in the presence of cationic polymers. Thus, it is clear that the present inventors were in possession of the concept of using a transfection reagent, such as cationic polymers, that provides improved results as compared with the use of electroporation when transfecting human ES-cells. As long as this concept was

in the specification, it does not matter that ExGen500 is the only example listed in the specification that meets these parameters. The specification contains an assay (in paragraph [0045]) that anyone of ordinary skill in the art could use to test other known chemical transfection agents for superior efficiency as compared to electroporation when transfecting human ES-cells. Enablement is not the issue here; the issue is simply whether one of ordinary skill in the art would understand that the general concept that the invention includes the use of chemical transfection agents that have superior efficiency to electroporation when transfecting human ES-cells. As indicated above, this concept is present in the specification and therefore the written description requirement of the first paragraph of 35 U.S.C. 112 is satisfied.

Furthermore, it is not understood why the examiner includes claim 7 in this rejection, as this claim specifies that the transfection reagent is a cationic non-lipid polymer transfection reagent, i.e., an ExGen500-type reagent. Thus, this claim does not encompass any transfection reagents other than that which the examiner agrees is adequately described in the specification. The same is true with respect to new claim 66.

Additionally, it is noted that claims 11-17, 69 and 70 all specify that the transfection reagent is a cationic polymer. Thus, these claims use the same language as is explicitly supported in paragraph [0043] of the present specification. Thus, this language is explicitly supported in the specification and certainly should not be subject to the present new matter rejection.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1-3, 7-9, 11-13, 16, 17, 59 and 60-63 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that, while the specification provides adequate support for the use of a polynucleotide that encodes a fluorescent protein or antibiotic resistant protein, the specification fails to describe any other species within the genus of gene expression altering sequences that show measurably different gene expression after introduction of the polynucleotide while retaining the pluripotent character of the cells as instantly claimed and encompassed by the claims with particularity to indicate that applicants had possession of the claimed invention. The examiner, in response to applicant's previous arguments, now states that the claims require that the polynucleotide that is introduced into the

hES cells be expressed, as well as retain the pluripotent character of the cells. The examiner states that paragraph 38 encompasses various genes that may or may not retain the pluripotent character of the transfected hES cells and that may be expressed only in differentiated cells. This rejection is respectfully traversed.

The claims have now been amended to clarify the intent, and so as to encompass all of the examples, such as those set forth in paragraph [0038] of the present specification. The recitation "without affecting the pluripotent character of the cells" has now been moved from the body of the claims into the preamble. Thus, the polynucleotide may be transfected into the cells without affecting the pluripotent character of the cells. That is not to say that the cells may not be caused to differentiate at a later stage. The fact is that the transfection does not, per se, alter the pluripotent character of the cells. Furthermore, the language of the claim has been changed slightly in order to specify that the gene expression in the embryonic cells after introducing the polynucleotide becomes measurably different from gene expression prior to introducing the polynucleotide. This does not require that the alteration of gene expression occur while the cells are still in their pluripotent stage. As explained in the specification and as

indicated by the examiner, the gene being inserted may only exhibit the altered gene expression once the cells have differentiated. Thus, the gene expression in the embryonic stem cells after introducing the polynucleotide, for example, after the cells are differentiated, becomes measurably different from gene expression prior to introducing the polynucleotide. The examiner is thanked for pointing out this unintended ambiguity. It is believed that the present language of the claims now better encompasses the disclosed invention, for the reasons pointed out by the examiner and discussed above.

Furthermore, new independent claim 65 has been added that is silent as to the nature of the polynucleotide that is transfected into the human embryonic stem cells. The feature that distinguishes the present invention from the prior art is the transfection efficiency grater than that obtainable by electroporation. Those of ordinary skill in the art know of many reasons why one would want to transfect a polynucleotide into human embryonic stem cells. It is not necessary for them all to be specified in the claim. Accordingly, claim 65 should not be subject to the present rejection.

For all of these reasons, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1-9, 11-17 and 59-64 have been rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The examiner concedes that the specification is enabling for a method for transfecting human ES-cells comprising introducing a polynucleotide that does not contain viral genes into a population of human ES-cells by transfection in the presence of a cationic non-lipid polymer reagent, wherein said polynucleotide encodes a fluorescent protein or an antibiotic resistant protein and, wherein the transfection efficiency is greater than that obtainable by electroporation. However, the examiner states that the specification does not reasonably provide enablement for the breadth of the claims that includes transfection of hES cells in the presence of at least one transfection reagent other then cationic non-lipid polymer reagents and the polynucleotide contains any gene expression altering sequence, such that the gene expression in the ES-cells prior to introducing the polynucleotide is measurably different from gene expression after introducing the polynucleotide while retaining the pluripotent character of the cells. This rejection is respectfully traversed.

First, as discussed above, the claims have now been amended in order to clarify the nature of the polynucleotide that is introduced. The claims no longer arguably require

that the expression be altered while the cells are still in the pluripotent state.

As to the use of transfection reagents other than cationic non-lipid polymer reagents whose transfection efficiency is greater than that obtainable by electroporation, the specification is fully enabling as it teaches an assay for determining whether any such agent is substantially better than electroporation, for example in paragraph [0045]. Many chemical transfection reagents are known in the prior art as alternatives to electroporation. However, with mouse ES-cells, electroporation provides the best efficiency and so it is the transfection means of choice. The present specification teaches that electroporation is not the transfection means of choice for hES cells, but that chemical transfection reagents may have unexpectedly superior transfection efficiency. While ExGen500 is the only one that was explicitly shown to have this superior efficiency, as discussed above with respect to the written description rejection, the present specification includes the concept that other chemical reagents will have such improved efficiency in human ES-cells, and particularly cationic polymer reagents. In view of the assay disclosed, it would not take undue experimentation for one of ordinary skill in the art to find additional such transfection agents. Accordingly, one of

ordinary skill on the art would know how make and use the invention without undue experimentation. This is all that is required of the enablement requirement of the first paragraph of 35 U.S.C. 112. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claim 16 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it recites "herpes simplex thymidine kinase" as a protein that can be encoded by the DNA, while claim 11 states that the DNA sequence does not contain viral genes.

Claim 16 has now been amended to delete reference to "herpes simplex thymidine kinase," thus obviating this rejection.

Claims 1-4, 6, 8, 9, 11-16, 36 and 59-61 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Smith when take with Ritter for the reasons of record. The examiner states that this prior art is reapplied because, although applicants have provided unexpected results with respect to utilizing a cationic non-lipid polymer reagent to transfect hES cells, this unexpected result is not found with respect to other transfection reagents that are encompassed by the claims. This rejection is respectfully traversed.

It is not understood why the examiner states that the present claims encompass the use of any transfection

reagent that does not include the unexpected result of an efficiency greater than that of electroporation. Every one of the present claims requires as a claim limitation that the transfection reagent be one that provides a transfection efficiency grater than that obtainable by electroporation. Thus, by definition, every claim encompasses only transfection reagents that possess unexpected results, i.e., result in a transfection efficiency greater than that obtainable by electroporation. No limitation of a claim can be ignored when making a prior art rejection. The fact that the claims are subject to a written description or new matter rejection is irrelevant when considering the prior art as every limitation of the claim must be considered and none can be ignored regardless of whether or not they are considered to be new matter. Thus, for example, if the present application is appealed to the Board of Patent Appeals and Interferences, the Board must be able to know what prior art rejections remain if it decides to overturn the new matter rejection.

As Smith only relates to electroporation and all of the present claims require a chemical transfection reagent with results better than that of electroportion, the present rejection is not applicable. Reconsideration and withdrawal of the present rejection is therefore respectfully urged.

Claims 1-4, 6, 9, 11-13, 15 and 16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Smith when taken with Gibco BRL catalog. The examiner states that Gibco makes obvious the use of LIPOFECTIN. This rejection is respectfully traversed.

As indicated above, the present claims require the use of a transfection reagent that provides results better than that of electroporation. Fig. 1 of the present specification shows that LIPOFECTIN does not fit this claim language and therefore the present claims do not encompass the use of LIPOFECTIN as a transfection reagent. Accordingly, no combination of Smith with Gibco can make obvious the present claims. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 5 and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Smith when taken with Ritter as applied above and further in view of Myers, which teaches that bioluminescent and chemiluminescent reactions are used as analytical tools in various analytical applications. This rejection is respectfully traversed.

Myers supplies nothing to the deficiencies of Smith and Ritter as discussed above. Accordingly, this rejection must be withdrawn for the same reasons as discussed above.

Claim 17 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Smith when taken with Ritter as applied above and further in view of Pascolo, which teaches the generation of mice that are double knockouts. This rejection is respectfully traversed.

Claim 17 is dependent from claim 11 and is, thus, allowable for the same reasons that claim 11 is allowable as discussed above. Pascolo fills none of the deficiencies of the primary references as previously discussed. Accordingly, reconsideration and withdrawal of this rejection is also respectfully urged.

In reviewing the prosecution history of this case, it was noted that claim 11 as originally filed specified that the DNA sequence transfected into the cells corresponded to "at least one of an enhancer, a promoter and a gene so as to alter gene expression in the population of embryonic cells …" In the official action of August 28, 2003, claim 1 was rejected as being indefinite and incomplete because, for the polynucleotide to be expressed it would be required to be operably linked to a promoter. Similarly, claim 11 was rejected as being unclear because a gene sequence would need to be operably linked to a promoter for expression of the gene expression. In response thereto the claims were amended to specify that the DNA sequence that is introduced is operably

linked to a promoter. It is now understood, however, that this amendment was ill-advised and that the original rejection was inappropriate. Accordingly, the claims have now been amended so as no longer to specify that the DNA must be operably linked to a promoter and claim 11 has been amended to reinsert that the DNA sequence may correspond to a promoter.

It is not necessary for the polynucleotide being transfected to necessarily be operably linked to a promoter. For example, a polynucleotide may be used for homologous recombination in order to knockout, insert or modify a desired gene from a mammalian cell (see, for example, example 6 in paragraph [0082]). In this case it is not necessary that the polynucleotide include a promoter as it can be directed by homologous recombination so that its expression will be controlled by an endogenous promoter. Furthermore, the polynucleotide may itself be a promoter which is inserted in such a way as to direct the transcription of an endogenous gene. In this case, the promoter need not be operably linked to another promoter. While a promoter may be present in the polynucleotide construct, it is not necessarily present. Accordingly, reconsideration and withdrawal of the rejection that originally appeared in 2003 and consideration of the claims as presently indicated are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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